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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/162,648	09/29/98	HISERODT J	

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EXAMINER	
STROUP, C	
ART UNIT	**PAPER NUMBER**
1638	2

DATE MAILED: 12/17/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/162,648	Hiserodt JC
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-20* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-20 of this application. Applicant's claims are to the use of two sequential cytoimplantations. Neither US provisional application 60/061766 or 60/061662 disclose the method of use of more than one cytoimplant.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 9 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant's claimed invention is to a method for treating cancer or eliciting an anti-cancer response in a human patient, comprising implanting at or around the tumor site a first cell population containing alloactivate lymphocytes that are allogeneic to leukocytes in the patient wherein said implantation is repeated within an interval of at least three days, one to eight weeks, or two to twelve months, and wherein said treatment results in one of the following effects in at least 30% of the subjects: substantial regression of tumor in size; lack of recurrence of a tumor after removal; or decrease in rate of formation of metastasis.

The specification discloses data from a phase I/II clinical trial for a single intratumoral injection of allogeneic lymphocytes sensitized against patient alloantigens comprising collection of peripheral blood mononuclear cells (PBMCs) from healthy non-familia donors via leukapharesis processed and resuspended in AIM V. PBMCs were also

removed from glioblastoma patients and processed with Mitomycin C to block response of the stimulator cells to the responder cells and resuspended with donor cells (20:1 to 10:1 donor cell: patient cell ratio) and tested for sterility (pg 35-36). Three days later a single dose of $3*10^9$, $6*10^9$, or $9*10^9$ implant cells were administered to 10 patients via direct intratumor injection utilizing endoscopic ultrasounds and resulting in a median survival of 11.5 months (range 4.2 to >21 months) (pg 41, lines 12-15). Patient 006 presented with increased tumor size and died 4.3 months after the one administration of said treatment (pg 40, lines 19-21). The specification only discloses histological data on one patient indicating apoptosis, but it does not indicate for any of the other 9 patients the occurrence of tumor size regression, lack of tumor recurrence, or decrease in the rate of metastasis (pg 41-42).

The specification also discloses a Fischer 344 Glioblastoma Multiforme rat model wherein said rat spleen cells were made into stimulator cells via isolation and irradiatation then mixed with allogeneic responder cells for three days at 37 degrees C, implanted intratumorally at day 10 and 17, wherein alloactivated cells from the same donor for both applications (Group 3) and from donors of different rat strains (Group 4), resulted in reduced tumor growth (Figure 3). Additionally, in group 3, 60% (3 out of 5) rats showed "essentially complete tumor regression" , while two showed tumor growth (pg 58, para 2; FIG 5). Further studies were conducted to determine the effect of tumor surgical excision after two cytoimplantations, wherein 2 of the 4 rats did not develop tumors, whereas 2 did, one at the site of resection and one elsewhere, thus indicating a metastatic case of tumor growth (A1045 #13) (Table 7, pg 60). Furthermore, the specification discloses a prophetic example for a clinical trial comprising the chemotherapy (Gemcitabine) versus cytoimplants five months apart in pancreatic cancer patients (pg 61-69).

Neither the clinical trial data on human cancer patients receiving one cytoimplant or the animal models in which rats received two cytoimplants indicate that at least 30% of the treated subjects displayed a substantial regression of tumor in size, a lack or recurrence of a tumor after removal or a decrease in rate of formation of metastasis because of a lack of a disclosure within the specification on the experimental conditions. For example, the

specification does not clearly state how many animals are in each group such that a percentage of a treatment outcome can be determined. It also states that two animals in group 3 did not eliminate the tumor (Figure 5) but that tumor progression was stabilized in the control group (Figure 1, group 1) or with a single implant (Figure 2, group 2). It is noted that Figures 1 and 2 refer to *in vitro* assays and not tumor growth for *in vivo* treatment, and that two of five animals in Figure 5 showed progressive tumor growth and not the asserted tumor stabilization. Additionally, Table 6 shows the results of two animals from Group 4 and not the claimed Group 3, and in Table 7 it is unclear as to if rats A1045 # 11,12,and 13 are part of Group 4, or a completely separate group. Additionally, with the exception of A1045 #13, there is no direct or implied data on metastasis occurrence, or lack thereof. Even in the event that the specification had provided a clear interpretation of said rat model data to support the claimed therapeutic outcome, said results do not directly correlate with treatment in a human. For example, Granger GA (US Patent 5,837,233) teaches the use of allogeneic lymphocyte implants into humans and rats for treating cancer and states that "Although these results in rats are of interest, their value in reasonably predicting what would be seen in a highly unrelated species, such as a human, is highly questionable in view of the considerable species diversity which exists, especially with respect to the immunological response to tumors" (col 2, lines 34-39). Therefore, it would require undue experimentation by one of skill in the art to extrapolate the results of an animal model for treating cancer in rats to results obtainable in humans, such that any predictable percentage of the subjects would be expected to exhibit a substantial regression of tumor in size, a lack or recurrence of a tumor after removal or a decrease in rate of formation of metastasis.

3. Claims 19 and 20 are objected to for the misspelling of "patent".

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 10 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10 and 16 recite the limitation "step c)" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-8, 10-14, and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Granger, GA (US Patent 5,837,233) in view of Slavin et al (US Patent 5,928,639 A), Feldhaus et al (US Patent 5,759,805) and Haugland, RP (1992).

Applicant's claimed invention is to a method for treating cancer or eliciting an anti-cancer response in a human patient suffering from melanoma, pancreatic, liver, colon, prostate, or breast cancer, comprising implanting at or around the tumor site a first cell population containing alloactivate lymphocytes that are allogeneic to leukocytes in the patient and comprising about $2*10^9$-$2*10^{10}$ donor PBMC and $1*10^8$-$2*10^9$ patient or 2nd donor PMBC's, wherein said implantation is repeated within an interval of at least three days, one to eight weeks, or two to twelve months (claims 1,

7, 8, 11, 12, 18). Said cell populations are obtained by a process in which donor lymphocytes are alloactivated by coculturing *ex vivo* with stimulator leukocytes for a period of about 48-72 hours, or are obtained by a process in which donor lymphocytes are alloactivated by coculturing *ex vivo* with stimulator leukocytes and harvested at about the time of initial alloactivation, via acridine orange or CD69 assay (claims 11, 17). The first implantation stimulates a response, such as an inflammatory or immunological response, against the tumor prior to the second implantation, and wherein said lymphocytes are activated against leukocytes of the patient or of a third-party donor (claims 2-6). Said methods also include a pharmaceutical composition comprising alloactivated lymphocytes allogeneic to leukocytes in a cancer patient packaged with written information for the treatment of the patient (claims 19, 20).

Granger et al teach a method for treating cancer, such as melanoma, pancreatic, liver, colon, prostate, and breast cancer (claim 37), in a human patient comprising implanting at or around the site of a tumor a cell population of about $2*10^9$-$6*10^9$ cells and comprising alloactivated human donor lymphocytes produced by coculturing said lymphocytes *ex vivo* with leukocytes from said patient at a ratio of 10:1 to 20:1 donor: patient cell ratio, for at least 48 hours, and preferrably 1-5 days (claim 37; col 7, lines 30-50). Treatment results in the patient generating a therapeutic or immunologic response against tumor growth and transplanted lymphocytes up to 74 weeks post implant(col 4, lines 1-35; claims 1-37). Granger et al also teach the use of a pharmaceutical composition comprising a sterile vial containing a unit dosage of mixed lymphocyte culture (a mixture of live alloactivated donor and patient lymphocytes) and bearing a label which sets forth information concerning the pharmaceutical use of the composition in treating a tumor in a human (col 6, lines 8-16). Granger et al does not teach the use of sequential implantations of cell populations or the use of a third party (or second) donor.

Slavin et al teach the use of multiple administrations of allogeneic lymphocytes, defined as lymphocytes taken from an individual not genetically identical to the patient into which the lymphocytes are infused, in a dose of about 10^7

cells for the purpose of eliciting an immune response against the tumor (graft-versus-malignant cell response)(col 3, lines 10-16; col 11; lines 40-45).

Haugland RP teach that acridine orange is a fluorescent dye utilized for assessing cell functions, such as metabolic processes (pg 172-173).

Jung et al teach that CD69 is an antigen on human lymphocytes expresed during the early stages of cell activation(abstract).

In light of Granger GA, Slavin et al, Jung et al, and Haugland RP, it would have been obvious to one of skill in the art to implant at or around the site of a tumor in a patient a pharmaceutical composition containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient and which elicit an immune response against a tumor and then to repeat said administration using the same donor cells or a second donor's cells. Said cell implant is obtained by a process in which donor lymphocytes are alloactivated by coculturing *ex vivo* with stimulator leukocytes for a period of about 48-72 hours or by a process in which donor lymphocytes are alloactivated by coculturing *ex vivo* with stimulator leukocytes and harvested at about the time of initial alloactivation, via acridine orange or CD69 assay, (Note the dose and interval between the two administrations are result effective variables which one of ordinary skill in the art could ascertain. It would also be obvious to package written instructions on the method of use of the pharmaceutical composition.) One would be motivated to do this to elicit an immune response against the patient's tumor cells wherein the patient's lymphoid cells identify both the donor lymphoid cells and the tumor cells as foreign (host versus graft rejection) and the donor lymphoid cells recognize the tumor cells as foreign (graft versus host response) (Granger, col 4,lines 12-24). One would also be motivated to repeat the administration with the same donor cells or a second donor's cells to increase the intensity of the immune response (Slavin et al, claims 1-37) or to prolong the treatment effect (Granger, col 4, line 4). There would have been a reasonable expectation of success because Granger, GA (US Patent 5,837,233) had already demonstrated that one administration of said cell population

intralesionally had resulted in up to 74 weeks of progressive tumor reduction (col 4, line 4; Figures 1, 2). One would also be motivated to use a CD69 or acridine orange assay to ascertain the time point in which T cells have become activated during co-culturing. There would have been a reasonable expectation of success because acridine orange assays are routine in the art in studying cellular metabolic processes (Haugland, pg 173) and CD69 expression is specific to early stage activated lymphocytes (Jung et al, abstract).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasmine Chambers, can be reached at (703) 308-2035. The fax phone number for this Group is (703) 308-0294.

Carrie Stroup

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